REMARKS

In this Amendment, claims 93, 144, and 148 are amended, and claims 106-120 and 150-151 are canceled.

Thus, after entry of this Amendment, claims 93-105, 144-145, 148-149, and 152-155 will be pending in the application.

Independent claims 93, 144, and 148 have been amended to recite a "synergistic combination." This amendment is supported by the specification at, for example, page 33, last line; page 34, line 23; page 35, line 19; page 36, line 15; page 37, line 14, page 38, and line 10.

No new matter has been added.

Entry of this Amendment is respectfully requested.

I. Summary of the Invention

The present invention provides a synergistic pharmaceutical composition for the treatment of cancer. The pharmaceutical composition, as defined in independent claim 93, comprises at least one chemotherapeutic agent and at least one immunoconjugate, the immunoconjugate comprising at least one maytansinoid compound linked to a monoclonal antibody or fragment thereof that binds to an antigen expressed by a cancer cell.

Most chemotherapeutic agents are not sufficiently active as single agents to cause long term disease remissions. Thus, chemotherapeutic agents are often combined with the desire to obtain compositions having increased anti-tumor activity.

Typically, cytotoxic drugs that have different mechanisms of killing are combined. Such drugs have different targets in the cancer cells and are called mutually exclusive drugs. Mutually

exclusive drugs either behave in an additive, synergistic, or antagonistic manner (Chou and Talalay, *Adv. Enzyme Regul.* 1984, **22**:27-55).

Preclinically, the effect of a combination of cytotoxic drugs can be studied *in vitro* on cell lines or *in vivo* with different tumor models. In such experimental systems it has been observed that most drug combinations show an additive effect.

In some instances however, the combinations show less or more than the expected additive effect. Thus, these combinations are "antagonistic" or "synergistic," respectively. Antagonistic or synergistic effects are unpredictable and are unexpected experimental findings.

II. Statement of Substance of Interview

On behalf of the Applicant, the undersigned thanks the Examiner for her time and for the helpful comments provided during the telephonic interview conducted on January 17, 2006. The required Statement of Substance of Interview is being filed herewith.

III. Claim Rejections Under 35 USC §103(a)

In the Office Action dated November 21, 2005, the Examiner rejects the claims as being *prima facie* obvious on the following grounds:

(1) At page 2 of the Office Action, the Examiner rejects claims 93-97, 102-110, and 115-120 under 35 USC §103(a) as being obvious over Lidor et al. or Rosenblum et al., in view of Chari et al., *Cancer Research* (1992).

(2) At page 4 of the Office Action, the Examiner rejects claims 93-97, 99, 102-110, 112, and 115-120 under 35 USC §103(a) as being obviousness over Lidor et al. and Chari et al., or Rosenblum et al. and Chari et al, and further in view of Schlom.

(3) At page 5 of the Office Action, the Examiner rejects claims 93-97, 99, 101-110, 112 and 114-119 under 35 USC §103(a) as being obvious over Lidor et al. and Chari et al., or Rosenblum et al. and Chari et al., and further in view of Liu, *Investigational Drugs* (1997) and Schlom.

(4) At page 7 of the Office Action, the Examiner rejects claims 93-98, 100-111, 113, 115-120, and 144-151 under 35 USC §103(a) as being obvious over Lidor et al. and Chari et al., or Rosenblum et al. and Chari et al., and further in view of Liu et al., *Proc. Annual Meet. Am. Assoc. Cancer Res.* (1997) and Schlom.

(5) At page 8 of the Office Action, the Examiner rejects claims 93-97, 99, 102-110, 112, and 115-119 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,208,020 in view of Lidor et al.

(6) At page 9 of the Office Action, the Examiner rejects claims 93-97, 99, 102-110, 112, 115-120 under 35 USC §103(a) as being obvious over Siegall et al., *Proc Annu Meet Am Assoc Cancer Res* (1997), in view of Chari et al, *Cancer Research* (1992).

(7) At page 10 of the Office Action, the Examiner rejects claims 93-97, 99, 101-110, 112, 114-120, 144, 146, 148 and 150 under 35 USC §103(a) as being obvious over Liu, *Expert Opinion on Investigational Drugs* (1997), in view of Watson et al., *Proc Annual Meet Am. Assoc. Cancer Res.* (1996) and Schlom.

(8) At page 12 of the Office Action, the Examiner rejects claims 93-97, 99, 101-110, 112, 114-120, and 144-151 under 35 USC §103(a) as being obvious over Liu, Watson, and Schlom, and in further view of Chari et al., *Cancer Research* (1992).

(9) At page 13 of the Office Action, the Examiner rejects claims 93-98, 100-111, 113, and 115-120 under 35 USC §103(a) as being obvious over Guchelaar et al., *Clinical Oncology* (1994) in view of Liu et al., *Proc. Annu. Meet. Am. Assoc. Cancer Res.* (1997) Lynch et al., *Journal of Clinical Oncology* (1997) and Liu, *Expert Opinion on Investigational Drugs* (1997).

(10) Claims 93-113 and 115-120 are rejected under 35 USC §103(a) as being obvious over Guchelaar et al., *Clinical Oncology* (1994), Liu et al., *Proc. Annu. Meet. Am. Assoc. Cancer Res.* (1997) and Liu, *Expert opinion on Investigational Drugs* (1997), and further in view of Schlom.

The Examiner acknowledges Applicants' remarks filed August 23, 2005, asserting that clinical or therapeutic synergism requires a balance of therapeutic and toxic interactions, and that synergistic behavior between two chemotherapeutic agents is unpredictable and must be established experimentally for each class of chemotherapeutic agents.

However, the Examiner contends that one of skill in the art would expect the claimed compositions and kits to have a therapeutic effect, and that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, citing *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

The Examiner also finds that the asserted synergism of the claimed compositions is not persuasive of non-obviousness because the present claims are drawn to *products*, as opposed to *methods*.

IV. Applicants' Response to Obviousness Rejections

Applicants respectfully traverse these rejections because the present specification shows that the claimed compositions have an unexpectedly superior property sufficient to rebut any *prima facie* case of obviousness, and in accordance with the law, *such evidence of unexpected properties is relevant to the non-obviousness of the composition.*

(A) The Examiner Must Consider Evidence of Unexpected Properties, and Such is Relevant to the Non-Obviousness of the Claimed Compositions

As set forth at MPEP §2142, the question of obviousness requires that the Examiner first establish a *prima facie* case of obviousness, and then consider any evidence of non-obviousness that Applicants may have to rebut that *prima facie* case.

As has been asserted in this application, and as discussed further below, the presently claimed compositions have the unexpected property of providing a synergistic treatment of cancer, and such is evidence that the presently claimed *compositions* are non-obvious. The Examiner's assertion that the evidence of unexpected properties can only support claims to methods of use, as opposed to claims to compositions, is legally incorrect. The Examiner is requested to appropriately consider the following law.

In the case of *In re Papesch*, 137 USPQ 43 (CCPA 1963), the Examiner took the following position, analogous to the position taken by the Examiner in the present case:

> Such contribution may properly be protected by claims to the mode of employing the compounds for their unexpected novel use, but does not support claims covering compounds which are structurally obvious and which also exhibit a family of properties and characteristics common to, and not differing significantly from, those of the homologue known and

> available in the prior art. ***An unexpected difference in a single property should not be adequate to support a claim for a novel, but obvious, homologue***.... Id. at page 46 (emphasis added).

However, both the Board and the Court found otherwise:

> As to the Examiner's view that in a case such as this the applicant should claim his invention as a process utilizing the newly discovered property, the board appears to have ignored it, properly we think. ***It is contrary to practically all of the above decisions wherein no fault was found with granting product claims***. Id. at page 52 (emphasis added).

This law was strengthened by the CCPAs subsequent decision in *In re McLamore*, 154 USPQ 114 (CCPA 1967):

> We there faced virtually the same argument the board is posing, however, and rejected it, namely, that under such a state of facts the invention should not be claimed as a compound but by some form of claim reciting properties, such as the method of lowering blood sugar.... See the last four paragraphs of our opinion wherein we stated ***we had also faced the same question in In re Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43, and answering it by approving claims to the compounds***. Id at 117.

The Federal Circuit has continued to endorse this reasoning. For example, in *In re Chupp*, 2, USPQ2d 1437 (Fed. Cir 1987), the Board took a position similar to the Examiner's position in the instant case:

> The board held that because the claims were limited to no particular weed or crop, 'the showing is not fairly representative of that which is encompassed by the claims.' Therefore, concluded the board, the evidence of superiority in corn and soybeans could not rebut the *prima facie* obviousness of the 'invention as a whole.' Id at 1439.

The Federal Circuit's response:

> ***Papesch held that a compound can be patented on the basis of its properties; it did not hold that those properties must produce superior results in every environment in which the compound may be used.*** To be patentable, a compound need not excel over prior art compounds in all common properties. Evidence that a compound is unexpectedly superior in one of a spectrum of common properties, as here, can be enough to rebut a *prima facie* case of obviousness. Id at 1439 (emphasis added).

Also see *Knoll Pharmaceutical Co. v. Teva USA Inc.*, 70 USPQ2d 1957 (Fed. Cir. 2004) and *Richardson-Vicks Inc. v. Upjohn Co.*, 44 USPQ2d 1181 (Fed. Cir. 1997), applying the law of unexpected properties to pharmaceutical composition and process claims alike, and finding no distinction as to the relevance of unexpected properties for a particular type of claim.

Therefore, under the controlling law, Applicants' unexpected properties are relevant to the non-obviousness of the presently claimed *composition*, and this evidence must be considered by the Examiner. That is, the Examiner must determine whether Applicants' unexpected properties are sufficient to rebut the *prima facie* case of obviousness for the present claims.

(B) The Presently Claimed Compositions Have Unexpected Properties

The arguments regarding unexpected properties are already of record in this application. (see the Table at pages 18 and 19 of the Amendment filed in response to the August 13, 2004 Office Action). This data, as summarized previously, is reproduced below for the Examiner's convenience. The data compares the results of treatment with individual chemotherapeutic agents (Groups 1 and 2) with the corresponding claimed compositions (Group 3).

	Treatment Groups	Therapeutic agents	Results
Example 2	Control	Untreated	Tumors grew rapidly to a size of about 900 mm^3 by day 28 post-tumor inoculation
	Group 1	huN901-DM1	Modest anti-tumor effect with a tumor growth delay of 4 days
	Group 2	Paclitaxel	Modest anti-tumor effect with a tumor growth delay of 4 days
	Group 3	huN901-DM1 and paclitaxel	Tumors disappeared with complete regression lasting 58 days
Example 3	Control	Untreated	Tumors grew rapidly to a size of about 900 mm^3 by day 28 post-tumor inoculation
	Group 1	huN901-DM1	Modest anti-tumor effect with a tumor growth delay of 4 days
	Group 2	cisplatin and etoposide	Modest anti-tumor effect with a tumor growth delay of 4 days
	Group 3	huN901-DM1 and cisplatin and etoposide	Tumor growth delay of 12 days (50% longer than what one would expect for an additive anti-tumor effect)
Example 4	Control	Phosphate buffered saline	Tumor grew rapidly to about 1000 mm^3 in 26 days
	Group 1	Docetaxel	Tumor growth delay of 8 days
	Group 2	huN901-DM1	Tumor growth delay of 20 days
	Group 3	Docetaxel and huN901-DM1	Complete tumor regression in all animals. In 3 out of 6 animals tumor was eradicated resulting in cures lasting greater than 200 days. In remaining 3 animals, tumor growth delay of 52 days (24 days longer than calculated additive effect).
Example 5	Control	Phosphate-buffered saline	Tumors grew to about 800 mm^3 in 44 days
	Group 1	Topotecan	Tumor growth delays of 12 days
	Group 2	huN901-DM1	Tumor growth delay of 34 days in 3out of 6 animals. Remaining 3 animals had complete tumor regression
	Group 3	Topotecan and huN901-DM1	Complete tumor regression in 5 out of 6 animals and tumor-free on day 78

Example 6	Control	Phosphate-buffered saline	Tumors grew rapidly to about 1000 mm^3 in 32 days
	Group 1	Paclitaxel	Tumor growth delay of 4 days
	Group 2	huC242-DM1	Shrinkage of tumor, but none of the 6 treated animals showed complete tumor regression
	Group 3	Paclitaxel and huC242-DM1	Showed greater anti-tumor effect resulting in complete tumor regression, with 3 out of 6 animals showing no evidence of tumor. The remaining 3 animals showed significant shrinkage in tumor.
Example 7	Control	Phosphate-buffered saline	Tumors grew rapidly to about 1000 mm^3 in 31 days
	Group 1	CPT-11 (i.e., irinotecan)	Tumor growth delay of 6 days
	Group 2	C242-DM1	Delay in tumor growth of 22 days
	Group 3	CPT-11 (i.e., irinotecan) and C242-DM1	Tumor growth delay of 38 days (10 days longer than calculated additive effect)

In view of the experimental evidence presented in this application (as summarized above), it is respectfully submitted that the presently claimed combination of an immunoconjugate and chemotherapeutic agent has the unexpected property of providing a "synergistic" treatment of cancer. ***The Examiner is respectfully requested to consider the present claims, which present the invention in varying scopes, individually with respect to the evidence of unexpected properties.***

In addition, submitted with this Amendment is a Declaration by Walter A. Blättler, which provides further literature and experimental evidence to show that: (1) mutually exclusive drugs, that is, cytotoxic drugs with different killing mechanisms, will have either an additive, synergistic, or antagonistic effect; and (2) that a combination of two mutually exclusive drugs will yield the same type of effect over the whole concentration range and at any ratio of the two drugs. For example, a combination of two mutually exclusive drugs that is synergistic, will yield this effect over the whole concentration range and at any drug ratio.

Thus, the present claims and the evidence of unexpected properties are commensurate in scope.

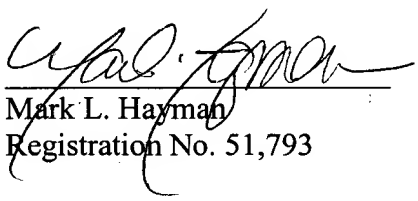
Withdrawal of the section 103 rejections is respectfully requested.

V. Conclusion

In view of the above, reconsideration of this application is requested. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge any unpaid fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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